EXHIBIT A

SpyGlass Group, Inc.

2 Spyglass Ct.

Annandale, NJ 08801

Expert Opinion

Report

Quality Assurance & FDA Compliance

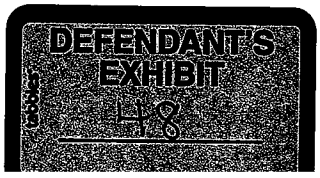
Actavis Inc.

Makers of Digitek

By

Mark G. Kenny

15 – June– 2010



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Expert Qualifications

The SpyGlass Group, Inc[1]. was contacted by the law firm Motley-Rice, seeking an expert in Quality Assurance and current Good Manufacturing Practice (cGMP)[2] to provide expert opinion in regard to a legal action against Actavis Inc. (formerly known as Amide), a manufacturer of drug products.

I have been engaged by Motley-Rice to prepare an expert report, participate in a legal deposition and testify as an expert witness in a trial. My expert opinion is based upon on over 35 years experience in:

- Running the Quality Assurance and Compliance Programs for multiple drug, medical device, diagnostics and consumer products manufacturing companies (from small start-up to large multinational companies)
- Objectively and fairly auditing hundreds of domestic and international medical products companies engaged in the development , manufacture and distribution of products regulated by the FDA
- Determining the potential adverse effects that noncompliance has on the product quality and the customer's trust in the product
- Reporting to senior management, risks associated with faulty control systems
- Understanding industry standards commonly used to comply to cGMP
- Reviewing quality records for the purpose of identifying potential violations to cGMP
- Investigating root cause of noncompliance and recommending reliable fix
- Creating effective corrective action programs for many companies in serious violation of cGMP, subsequently eliminating public health risks
- High level consulting for major medical industry companies

The complete CV for Mark G. Kenny is included as *Appendix A – Mark G. Kenny CV*. The following summarizes my related assignments:

- SpyGlass Group Managing Director (6 years)
- Corporate (Regional) Quality Assurance Director for Johnson & Johnson (J&J) Corporate (Headquarters) (8 years)
- Executive Director of Quality Assurance and Management Board Member for Direct Access Diagnostics (J&J) – Home diagnostic products, including home HIV test (3 years)

[1] Quality & Compliance Consulting Group – website: www.spyglassgroupinc.com
[2] 21 CFR Part 210 and 21 CFR Part 211 Current Good Manufacturing Practice for Manufacturing, Processing, Packing, or Holding of Drugs and Finished Pharmaceuticals

- Executive Director of Quality Assurance and Management Board Member of Advanced Care Products (J&J) – Monistat and other OTC products (3 years)
- Director of Quality Assurance and Labs for IOLAB (J&J) – Intraocular Lenses, Electro-Mechanical Devices for Ocular Surgery (3 years)
- Director of Quality Assurance Compliance for Ortho Pharmaceutical Inc (J&J) – Oral Contraceptives, dermatological drug products, monoclonal antibody drug products, antifungal drug products (3 years)
- Director of Quality Assurance (External Manufacturing) Johnson & Johnson Consumer and Healthcare Products – women's healthcare drug products, dermatological products, wound healing products, medical device products (5 years)
- Validation & Pilot Project Engineer for Ethicon Inc. – wound closure devices (4 years)

Achievements include:

- Authored Multiple J&J Corporate Policies – including sterilization
- Partnered with the FDA and lead the GMP compliance effort & late stage development team for the First FDA Approved Home HIV Test
- Lead GMP Compliance for First FDA Approved Monoclonal Antibody Therapeutic Product
- Lead Assessor for Multiple J&J Acquisitions
- Reversal of negative GMP Compliance trends for multiple companies
- Lead auditor on many high profile compliance situations
- Developed hundreds of Quality Assurance and System Procedures
- Developed multiple Master Validation Plans and Master Compliance Plans
- Johnson & Johnson lead representative on HIMA (Health Industry's Manufacturing Association) cGMP Committee and CHPA (Consumer Healthcare Products Association: formerly called Non-Prescription Drug Manufacturer's Association) on the Stability Testing Committee
- Authored Multiple J&J Corporate Worldwide Guidelines
- Lead the GMP compliance preparation for multiple companies
- During FDA Inspections, defended the GMP Compliance Program for multiple companies
- Throughout J&J domestic companies, became the second Quality Assurance & Compliance head to be appointed to a company's Management Board
- Lead two different company's Quality & Compliance Programs from being rated "worst" to "best"
- Established a consulting company comprised of former senior executives in Medical Products Technology, Quality Assurance, Compliance, Operations and Regulatory Affairs
- Awarded seven (7) Johnson & Johnson Leadership Awards for GMP and Quality achievements – this is J&J's highest personal award

Introduction

The SpyGlass Group, Inc. has determined that Actavis/Amide (hereafter referred to Actavis) was not complying with the FDA legal requirements for current Good Manufacturing Practice (cGMP or GMP) for at least the period of time, starting in 12/1/2004[3] and ending with their Permanent Injunction of Nov. 14, 2008[4]. Because of the serious violations of GMP, for this period of time, the production, control and quality processes for Digitek were not able to consistently and reliably manufacture products that meet legal requirements. During this period of time, the records demonstrate that Actavis released product that did not meet product specification and as such were adulterated[5].

Their troubled past included a 1992 FDA Consent Decree. Then there was some period of time (1993 through the 1st Quarter of 2004) when FDA records indicate that the operations were GMP compliant. There were several FDA adverse inspectional findings notices (commonly called FDA Form 483 or just 483) issued over this period of time; however, Actavis/Amide corrective action appeared to have satisfied the FDA's concerns. Then for a period of six (6) years, beginning in 2004 until their 2009 Permanent Injunction, there appears to have been a significant breakdown in their Quality Systems and overall compliance to GMP. As a result of multiple FDA site inspections over this six (6) year period, Actavis was issued multiple FDA adverse finding reports. As a result of not taking swift and effective corrective action to the FDA 483s, the FDA escalated their public concern by issuing numerous FDA Warning Letters (*See section A Primer on cGMP FDA Regulations & Important Quality Assurance Concepts* for more information on Warning Letters.) Actavis did not effectively correct the deficiencies identified in the FDA mandates. After being given every opportunity to correct their deficiencies, through the legal process a Permanent Injunction was served and Actavis stopped manufacturing and release drug products from the affected sites. This type of severe legal action on a United States drug company is exceedingly rare. My review of the evidence confirms the good judgment of the FDA.

A detailed evaluation of the cGMP Compliance history of Actavis was performed by the Spyglass Group for the period of 2006 – 2008[6]. The FDA conducted five (5) inspections over this period that resulted in over 40 significant observations and two (2) Warning letters and a final Consent Decree for Permanent Injunction.

In this Expert Report, the SpyGlass Group has classified the FDA observations into five (5) system categories:

1. Quality System
2. Facilities & Equipment Systems

[3] FDA Form 483, Issued to Divya C. Patel (President), District FDA Office in Parsippany - NJ, 12/1/042004
[4] Plaintiff's Exhibit #82, Complaint of Permanent Injunction, 11/14/08
[5] Plaintiff's Exhibit #124 – Definition of an adulterated drug, US doc. 351.
[6] Appendix D Summary of FDA Observations & Events

3. Production System
4. Laboratory & Control System
5. Regulatory Requirements

Beginning in 2004, Actavis produced products using processes and control systems that were shown to be unreliable. To illustrate this conclusion, in only a two (2) year period (primarily 2007-2008) there were over:

- 300 Out of Specification (OOS) incidences (2007-2008)
- 300 Formal Investigations (2007-2008)
- 200 Deviations (2007-2008 -over a 12 month period)
- 20 Rejected Batches (2006-2007 – 12 month period)

The number and type of issues indicate that the company operated in a state of nonconformance for an extended period of time.

Additionally, a review of some of the investigations associated with Digitek identified significant issues that are specific to many batches, including double thick tablets.

Management at Actavis was aware of this and other GMP issues but failed to adequately correct the problem. When comparing 2007 to 2008 for Laboratory OOS, there was no improvement in numbers. When comparing 2007 to 2008 for Investigations, the number doubled for 2008. They performed inadequate investigations into the nonconformances; therefore, they were unable to implement sustainable improvements.

The detailed analysis of the FDA findings determined that each of these systems had numerous observations. There was consistent inadequate corrective action; therefore, there was a pattern of repeat observations. Critical systems that control the Quality of the product were substantially and consistently out of compliance and operating in a high risk environment. There was no apparent attempt to mitigate the product quality risks through extra testing, inspection, etc.

My independent findings have confirmed the FDA issues. Additionally, many more issues were identified that demonstrated that Actavis was critically noncompliant with GMP regulations and released product that did not meet GMP. The product manufactured during this period of time was adulterated (See Page 12 for description of adulterated drug.)

It is my opinion to a reasonable degree of certainty and based upon my experience and qualifications and after reviewing hundreds of pages of evidence that Actavis management's actions or lack thereof, demonstrate that legal compliance with Federal Regulations as stated in the GMP section of the Code of Federal Regulations was not one of their business priorities. Over at least a six (6) year period, Actavis failed to meet legal and patient obligations.

Work Plan

Approach

- Review documented evidence applicable to the scope of the assignment
- Prepare an expert witness report that documents my findings
- Participate in future legal proceedings which may include deposition(s) and a trial process

Quality and Control Systems

- To determine whether or not Actavis was operating within cGMP FDA regulations

Product Quality

- To determine whether or not Digitek (digoxin) tablets made over the period of 2003 to 2008 met the requirements for identity, strength, quality that they purport to have and were fit to be released for sale
- To determine whether or not Actavis had or had not released adulterated product

A Primer on cGMP FDA Regulations & Important Quality Assurance Concepts

What is Drug c GMP?

Current Good Manufacturing Practices (cGMP or more commonly called GMP) is a law that was established in the Code of Federal Regulations. It represents the minimum requirements in the Drug Industry for producing a product that meets all specific requirements for identity, strength, quality, and purity. The law was originally drafted for comment by the FDA using industry acknowledged experts. Industry experts then commented on the content of the draft proposed regulation and in an iterative process, a law was established that outlines the requirements for every drug manufacturer to follow. It has been continually improved (via the same methodology, i.e. industry participation) since its approval. My opinion (which is shared by most industry Quality & Compliance leaders) is that it is a well designed document and of great help in ensuring that patients and customers receive 100% safe and effective drug products. In fact, most Quality & Compliance leaders place GMP in business terms; frequently refer to GMP as "good business practices." Likewise, it is my experience that the FDA understands the business and fairly and impartially uses a heavy-hand only when they fear public safety. In these high-risk situations, they continually escalate their concerns until all public risks are resolved.

Why is GMP Important?

It is important to understand that the term "Good" is somewhat misleading, GMP is the legal minimum and it is not optional. My opinion (which is shared by most industry Quality & Compliance leaders) is that significant breakdowns of the Quality and Control Systems (established in this regulation) will inevitably result in serious product quality risks; more specifically, "bad product" being released to the American public.

Why is the FDA Requirement of Investigating and Corrective Action So Important?

All of the controls established in the GMP Regulation are important; however, some are more important than others. The concept of Corrective Action and Preventive Action (CAPA) is critical.
When errors (referred to as nonconformances) are discovered in any of the Product Quality and/or Control System, by law, industry must investigate the issue. This is common sense to most people, i.e. when you find a problem you need to understand the seriousness of the problem and resolve the situation accordingly. Some nonconformances are important but not urgent. Other nonconformances require immediate investigation, including notifying top management. This practice is somewhat similar to the triage procedure used in a hospital emergency room. For example, if manufacturing equipment were to produce products that had cosmetic issues (e.g. slight crooked printing) of the carton lot number; this is important

but not necessarily high risk. The operator has the authority to make an immediate adjustment on the equipment and (with Quality Assurance oversight) inspect the product made, determine when the problem occurred and potentially cull out the defective cases for immediate reinsertion and rework. This type of occurrence would generally not require the immediate notification to top management. On the other hand, if defective tablets (for example double thick) were being discovered at any point in the manufacturing process, immediate actions would result. This is a highly disciplined procedure. It is likely that many of the following actions would be performed;

A. The production line would be stopped and not restarted until a complete investigation was performed (in accordance to a detailed control procedure).
B. This category of defect, i.e. oversized or potentially mixed tablets, creates the highest order of concern for the company. Any suspected suboptimal control system that could result in this type of defect is what keeps Quality Assurance Directors up all night.
C. The Manager of Quality Assurance and Manufacturing would be notified immediately
D. A formal and documented investigation would begin (in accordance to another detailed control procedure)
E. Based upon the preliminary investigation, that lot number would be placed on hold and segregated, identifying the product as potentially defective. Additionally, the batch would be identified in the computer inventory control system as on Hold or Quarantined, thus eliminating any chance for the premature release of the potentially defective product. Classifying the product lot as "On Hold" and later reclassifying a product lot as "Accepted" is a key control step. Quality Assurance is the only one that has the electronic "key" to change these product lot classifications. Unless a worker purposely mishandles defective product, it is almost impossible, in current computer inventory control systems, to generate the necessary paperwork to release a batch for sale.
F. A full-scaled documented investigation would follow, ascertaining the specific (root) cause of the nonconformance. The investigation would extend into many of the control systems within the company, far beyond some of the obvious potential causes. The investigation would also be extended to other batches. All potential sources would be systematically investigated to ensure that the problem is not more widespread. As part of the investigation, a determination would be made as to the acceptability of the batch.
G. After the documented investigation has determined the root cause, a specific documented corrective action program would be designed and deployed.
H. A Material Review Board (or equivalent) would meet to discuss the adequacy of the investigation and appropriate next steps.
I. If it is determined to be a risky practice that cannot be quickly corrected then the line would be stopped indefinitely until the risk is eliminated.
J. Depending upon the situation, the production line would be revalidated after the corrective action is complete.
K. Ultimately, QA will decide the outcome. Release of product is not a democratic process.
L. The product would have been destroyed.

What are the Results of Not Following GMP?

There are many potential outcomes, all are adverse. The following identifies a few of these adverse outcomes:

A. FDA Issues - FDA inspections have a reasonable probability to discover the lack of GMP Compliance when problems are more widespread. It is important to understand that no matter how long the FDA spends at the site, they do not have the capability to identify all of the problems. During an inspection, they determine the seriousness of the company's practices and determine the reporting method. When there are issues then the FDA reports the observations using a form – FDA Form 483. Should the situation warrant it, the FDA will continue to escalate their actions from an FDA Form 483 notification to more severe notifications, including: Warning Letter(s), Consent Decree, or worse, including the Permanent Injunction. A Warning Letter[7] is a communication to the firm that has been reviewed within several levels of the FDA, including the district office and the office of compliance at FDA's headquarters. The Warning Letter generally states that the firm has made products that are adulterated, violating the Food, Drug, and Cosmetic Act and that the firm has a very limited amount of time to address the problem(s) before the FDA takes further regulatory action against the firm, the adulterated product, and responsible individuals. Permanent Injunction is highly rare and represents the FDA's highest order of concern. Manufacturing Problems – GMP describes fundamental controls that are necessary to be in business. Most of the top companies in the world (regardless of product category) practice these principles and deploy them exceedingly well. Those companies that do not are likely to have significant lapses in sustaining these procedures and are doomed to have product recalls. Companies that experience GMP problems are continually "fighting fires" and are constantly being faced with nonconforming product and nonconforming practices.

B. Product Quality – Product quality will always suffer when GMP is not established. The worse the systems, the worse the problems. Each product defect (originating with complaints, production line, packaging line, etc.) needs to be formally investigated. When a company is constantly fighting these types of fires, there are never enough people to manage the fires. The result is that the problems are ignored or the investigations are superficial, having little chance to determine the root cause and less chance to implement an effective and sustainable corrective action. The lack of effective control systems is the common root cause of almost all product defects. The lack of effective control systems will result in the release of product that does not meet specification, adulterated and are unfit for human use. When this type of product is discovered or the quality is suspect, a responsible company will Recall the product. If the company does not recall unsafe product, the FDA can legally seize all affected product.

[7] http://www.cgmp.com/warningLetter.htm

What are Some of the Critical Systems & Controls in Drug Manufacturing?

Batch History Record: This is a compilation of all of the vital records and results that provide evidence that the production lot/batch was manufactured and tested in accordance to approved procedures, test methods and specifications. It is also evidence that a batch complies with any FDA submissions. It is a stand-alone document, which means that it should be understood by any experienced reviewer without any significant explanations. It must be complete. The document must include the records previously mentioned plus any exceptions. Exceptions would include issues that were encountered during the manufacturing or testing of a batch. For example the following documentation is required to be in the batch records: out of specification reports, CAPA reports, rework or salvage records, etc. The final control step, before the product is released to market, is the independent Quality Assurance review. This person's responsibility is to review the records of the batch and ensure that it meets specification and was produced and tested in accordance with approved procedures. Quality Assurance then certifies in writing that the product was manufactured and tested in accordance to the approved procedures and the test results meet all specifications.

Out of Specification Test Result (OOS): If a lab analyst performs a test and discovers out of specification results, then the analyst must follow a strict procedure which involves a formal and documented investigation. The initial first results cannot be automatically disregarded. This FDA required procedure has built in controls to ensure that the final test results are valid. An OOS is a significant occurrence that requires critical thinking and investigation to properly resolve. The documentation associated with the event must be carefully documented in accordance to the procedures. Failure to follow the OOS procedure will yield results that may be incorrect, ultimately allowing unacceptable product to be released to the market.

Nonconformances: When manufacturing or Quality assurance action does not meet the approved procedure then a nonconformance occurs. When a test is performed and the results do not meet the specifications and/or the documented requirements, then a nonconformance occurs. All nonconformances are required by law to be investigated and handled in accordance to approved procedures to resolve the problem.

Good Documentation Practice: This is an informal term for highly formalized controls that are included in the GMP. The following highlights some of the more common sense aspects of good documentation practice. All recorded information must be clear, legible and understandable. When an error is made by an associate, the error must be handled in accordance to procedure. There will be signed and approved signatures next to every change of results. There is a legal code of ethics stated in the GMP that all information including dated signatures must be honest. All documents requiring approval, e.g. CAPA, must be signed by all of the technical and management associates as required by the procedure. There is no exception to this rule. Any records that are not honest are falsified records. Any unapproved/unsigned and undated documents are not acceptable records and almost unusable. Quality Assurance has the responsibility in all steps of the process (raw material receipt and testing, inprocess inspection and testing, product manufacturing and packaging, finished product testing, etc.) to continually review the records as

production progresses. The final Quality Assurance batch history record review is intended to discover good documentation practice nonconformance and hold the batch until a documented investigation is conducted, again in accordance to approved procedures. This is not a nice to do, it is the law. Although the term Good Documentation Practice is not specifically mentioned in this expert report, it is important to understand and have an appreciation for the rules governing records.

Complaint Handling: Each complaint must be properly investigated in accordance to GMP and other FDA guidance documents. This is a disciplined procedure that requires a series of formal events to take place. These steps are intended to determine the potential seriousness of the complaint. The events associated with an investigation may typically include (but is not limited to):

- Examination and chemical testing of the complaint sample
- Examination and testing of product retain sample(s) (retained product samples are required to be selected from every batch and stored in a controlled manner, intended to help investigations into future problems)
- Review of prior complaints with the specific batch
- Review of prior complaints with this specific product and similar products if there is an issue, it must not be automatically assumed that the problem is only affecting the complaint batch.
- Trend analysis
- Inspection of the Batch Record and other records
- Interviews with manufacturing and Quality Assurance
- Review of studies performed, for example equipment qualification studies, process validation studies
- Review of the adequacy of the current procedures and specifications
- Review of the stability testing results

If the investigation determines that there might be unsafe product in the marketplace, then the investigation must be escalated to top management and a recall decision must be considered. This must be conducted in accordance to procedures and FDA Regulations. Some of the activities and documentation may have to be submitted to the FDA for their review.

Managing Contract Manufacturers

It is common for companies to have their products made under contract by a company that specializes in the manufacturing and testing of drug products. The relationship and responsibilities between both organizations is normally established, in part, within a mutually approved Quality Agreement. The Quality Agreement is formally approved by both parties. The agreement itemizes every critical control system and the corresponding responsibilities. The agreement identifies methods to communicate and approve documentation and product release. The FDA requires that companies have well designed control systems to manage their contractors, including Quality Agreements, in place prior to the production of any products.

The contracting company is required by the FDA to formally qualify (i.e. approve) the contractor based upon objective evidence that the contractor is in full compliance with GMP. Normally a GMP audit is conducted at different stages, for example: initial qualification, periodically thereafter (typically once every year or two) and for cause (i.e. problem related). The GMP audit is a highly structured event. An auditor or a team of auditors spends a minimum of one day reviewing documents and records to ascertain the relative level of GMP compliance (similar to an FDA inspection.) A detailed report is then written that includes: scope of audit, itemized areas covered and exceptional findings. The findings are generally categorized by risk level (e.g. major and minor). A final review meeting is held and the findings are reviewed. The audit report is then sent to the contractor who is required to reply to the audit and indicate their proposed corrective action to every nonconformance to GMP regulations. The next audit would review and verify that the corrective action has been effective. All of the previous activities must be done in conformance to a written procedure.

What is an Adulterated Drug?

A 1962 Amendment to the cGMP provision of the FD & C Act, Section 501 (a) (2) (B) states "A drug...shall be deemed to be adulterated if...the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

This is an important concept because this FDA Amendment dispels any misconception that adulterated product is limited to out of specification test results of a finished product. The FDA has stated that product is adulterated when the procedures, controls, raw materials, components and/or practices do not comply with GMP. There is a recognition that quality products do not happen by accident. It does not happen by merely testing the product at the end of the manufacturing line. It is the result of a highly disciplined approach to establishing controls and procedures using the minimum standards of the GMP. This concept is built on the premise that quality is built into the product rather than tested into the product.

a. Actavis Corporate Culture & Management

There has been consistent evidence that Actavis Management did not understand the importance of GMP and its direct link to product quality. It appears that their lack of understanding begins at their website[8]. Actavis defines their Manufacturing Practice as based upon GMP which is stated as: "Good Manufacturing Practice (GMP) is a regulatory guideline imposed on all manufacturers of pharmaceuticals…" This statement is not correct because GMP is a Federal Law, not a guideline. This is an important distinction.

It is my opinion to a reasonable degree of certainty that management never displayed an understanding of the legal requirements of GMP. In spite of experiencing significant issues, management never altered their flawed strategy.

The significant issues include:

- FDA Form 483
- FDA Warning Letters
- Alarming number of Quality problems
- Product Recalls
- Breakdowns in their Quality System.

It is my opinion to a reasonable degree of certainty that they were highly resistive to systematic change, appearing sure that minor improvements would resolve all of their issues. This was a flawed strategy; their arrogance resulted in managing a drug company that operated at a high risk level.

This 2008 statement by Jacob Haroon (Actavis Director of Regulatory Affairs at the time of the email) describes the situation quite well: "This is all rather sad. Looks like some very basic GMP knowledge was lacking."[9] Unfortunately, it is the patients that could suffer from this risky situation.

It is my opinion to a reasonable degree of certainty that Corporate and QA management were not knowledgeable of the cGMP. Additionally, there was a lack of understanding of the regulatory approval process since many drug products were made and sold without approved NDA's /ANDA's.[10] The Actavis Senior Director of Compliance and former FDA Director of Investigations for New York State wrote[11] that the potential 483 items could include:

- The Quality Unit failed to do its job
- The Quality Unit has released batches of drug products that failed their specifications

[8] http://www.actavis.com/en/products/manufacturing/good+manufacturing+practice.htm
[9] Plaintiff's Exhibit #147 – Email Subject: Form FDA 483 RV.pdf, Jacob Haroon, 5/27/ 2008
[10] Complaint for Permanent Injunction, Case 2:08-cv-05656-SDW-MCA, Christopher Christie (United States Attorney), Filed 11/14/2008, p 11
[11] Exhibit Plaintiff's #146- Email Subject: Totowa Potential 483 items and comments, Wanda Eng, 4/17/2008

- The Quality Unit failed to adequately conduct deviation investigations in that the root cause was not determined
- Failed to file NDA Field Alerts associated with confirmed stability failures
- Failed to reject products which did not meet in-process and finished product specifications
- The Quality Unit released products for distribution prior to the completion of the deviation investigation
- Continued to manufacture and ship unapproved DESI drug products after receipt of a Warning Letter requesting justification to market products
- Tested product into compliance and discarded the OOS results; using only retest results without adequate justification
- Failed to have adequate stability programs
- Laboratory investigation of OOSs were inadequate
- Actavis' filings submitted to the FDA to widen specifications when a product fails to meet specification
- Many manufacturing processes are invalidated by the high percentage of stability failures
- Actavis produced digoxin tablets with black spots of unproven origin
- Actavis produced digoxin, a toxic product with double, triple and thin tablets: lots were not rejected

The Actavis Senior Director of Compliance and former FDA Director of Investigations for New York State also wrote (in full capital letters) that potential 483 items could include:

- "OUT OF CONTROL"
- "LACK OF RESOURCES"
- "LACK OF EXPERTISE"

The FDA stated in the 2006 Warning Letter[12]:

- "Several of the observed deficiencies were long-standing, and there is no indication of how or why the lack of compliance was not identified by your firm"
- "why it was allowed to continue for such an extended period of time"
- "Does your firm have any insight into this situation"?

Mylan stated[13] in their 2006 visit to Actavis that there was a "shortage of qualified personnel".

Actavis did not respond to the critical FDA observations in the August 2006 FDA 483 in a timely manner. Ten (10) months after the 2006 inspection the following was a status of their corrective action implementation in their Totowa Action Plans[14]:

- 5 not corrected

[12] Plaintiff's Exhibit 229 – Warning Letter, Douglass Ellsworth, August 15, 2006
[13] Mylan Audit, Subject: Final Corrective Action Memo, from R. Pinnell, 1/23/2008
[14] Exhibit Plaintiff's #137 – Totowa Action Plan (August 2006 GMP Inspection Totowa), Not dated - estimated July 2007

- 6 partially corrected

In the same document it states that more than half of the August 2006 observations had not been corrected. This includes FDA's observations:

- Failure of the Quality Unit to fulfill its responsibilities
- Quality Unit failed to assure that lab notebooks include all data generated et al.
- SOPs not always followed
- Master production and control records do not include complete sample and procedures

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Actavis Understanding of the Gravity of the Problems

The FDA required that Actavis respond to each adverse notice (483 and Warning Letter). The Actavis letters to the FDA represented two areas: 1. Areas promised to correct and 2. Areas that were already corrected. In some ways, they can be thought of as promissory notes and certification of corrective action. Actavis repeatedly failed in this regard. They frequently made promises that were not kept and improvements and corrective actions that were not adequate or sustainable. After the submission of Actavis' reply to the FDA, there are abundant examples where their reply is not correct. For example, in the Revised FDA Warning Letter – E. Main St. Little Falls - Dated 2/1/2007[15] in regard to Actavis' disagreements with the FDA position, the FDA stated:

- "Your response provides no assurance that the records and conditions of manufacture and testing of each such lot of drug products released and marketed by our firm will be evaluated to assure that the released drug products have their appropriate, identity, strength, quality, and purity
- "In fact, we do not agree with assertions in your August 29 and 30, 2006 letter that certain of the observations listed on the FDA 483 are not accurate"
- "...we are concerned about the quality of the of drug products that have been released from your facility under the serious lack of cGMP controls found during the inspection."

Lack of Timely Remediation

In the Actavis 5/20/2008 Memo to Senior Management[16] – The Actavis scribe summarized the FDA Inspector's statements: "from a Quality Systems standpoint, there was a Total Failure." Additionally, the scribe documented that the FDA stated:

- Do not fix broken systems – get new systems
- (Need) Improved infrastructure
- Investigations on the (past) 483 still not complete
- Health hazards on recalls are delinquent

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[15] Plaintiff Exhibit #25 – Revised Warning Letter, 2/2007

[16] Exhibit Plaintiff's #106 - Subject: FDA Little Falls Inspection Closeout – May 20, 2008, Garret R. Woolan – Scribe, 5/20/2008

- We (FDA) get very nervous when you tell us that you are releasing product using current Quality Systems
- One (QA) person was signing off in multiple locations on the batch (this occurred on the Digoxin "double tablet" Investigation). Erin (FDA representative) considered this a very important Observation – additional review of this Investigation may have stopped release of the batch)
- It was "premature to be releasing product"
- The FDA is concerned about product still on the market that was made in Little Falls using similar systems that had failed
- That FDA has concern about the 48 products with no impurity profiles
- The tougher issues are - What is the approach to handling product made under these substandard systems?
- The FDA questioned the validity of Actavis' Batch Record Review process because the FDA had found important nonconformances (e.g. black spots) that were not included in the record. A review of an incomplete batch history record provides a false sense of security.

February 2009 - Quality System Improvement Plan (QSIP)[17]

A Quality System Improvement Plan was developed with the aid of consultants. This QSIP was started in the 4th Quarter 2008, three (3) years after the first (in a series) of 483 and Warning letters. Well run firms would have responded immediately after the first 483 in 2006. Furthermore, this would be an alarm that the major systems are not in control and product quality might be adversely affected. These firms would have immediately ordered an intensive internal audit and determined the risk level of each Quality System component. A comprehensive action plan would then be established. In the case of Actavis, it required the hiring of a Quality System consulting firm to begin this evaluation and improvement process (Committee started 11/20/08).

The QSIP identified 201 Observations:

1. Materials Management – 27 Observations
2. Facilities & Equipment – 49 Observations
3. Production Controls - 22 Observations
4. Packaging & Labeling – 15 Observations
5. QC Laboratory – 14 Observations
6. QA – 45 Observations
7. Actavis R&D – 29 Observations

As of February 2009, there were still about 24% open observations, over three (3) years after the 2006 FDA 483.

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[17] ACTAV 000484606 – Quality System Improvement Plan, 2/26/2009

Ineffective Internal Audit Process

The Internal Audit Procedure is designed to provide an independent audit of the company's relative compliance to GMP. It provides management with objective information on GMP compliance. Many of the problems associated with the FDA issues should have been identified through the internal audit procedure and formally communicated to management. This is normally an annual event intended to identify GMP risks and provide evidence that the contractor is in a state of control. It also authorizes the continuance of business as usual (unless critical issues are identified during the audit.)

A review of an internal audit[18] (conducted on 1/24/2008) identified issues, most of which were not critical and were specifically related to work instruction steps in a procedures and associated records. There is no evidence that the auditor identified any of the systemic issues that were later identified by the consultants in the 4th Quarter of 2009. It would not be expected that less intensive audit would find all of these observations; however, many of the fundamental issues should have been identified as requiring improvement, providing a red flag to Actavis management. This aligned with the FDA. In the Warning Letter[19] which stated: "Several of the observed deficiencies were long-standing, and there is no indication of how or why the lack of compliance was not identified by your firm"

Senior Management Top Priority – Not on GMP

In a presentation[20] at a company meeting in February 2006, the Executive Chairman for Actavis presented in a slide show: "How Do We Achieve Success?" This will be achieved by Low Cost and most importantly Speed. There is no mention of GMP or Compliance in this presentation.

Actavis Corporate Culture & Management
SpyGlass Group Summary

It is my opinion to a reasonable degree of certainty that:

- The aforementioned examples indicate the gravity of their situation. The environment created by management within the company fostered noncompliant behavior. The abilities and motivations of management have to be questioned based upon their actions.

- The type and frequency of issues indicate that an effective Quality System was never sustained and their GMP legal obligations were never fulfilled. It is highly disturbing that there was a lack of understanding and urgency to these serious issues even after 16 years of significant FDA actions.

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[18] Plaintiff's #175: M. Patel, Email Subject: Regarding internal cGMP audit, 1/25/2008
[19] Plaintiff Exhibit #25 – Revised Warning Letter, 2/2007
[20] Exhibit Plaintiff's #92 – Presentation at a Feb 2006 Sales Meeting, Not Dated

b. Product Quality & Quality Systems

This section of the report analyzes some of the situations related to Product Quality Nonconformances, Deviations and OOS.

The following highlights some of the major Product Quality issues and the alarming rate of OOS, Investigations and Deviations. Items 1 and 2 are specifically for Digoxin. Subsequent Items are general and for all products.

1. There were multiple incidences of Double Thick and Overweight Digoxin Tablet lots:
   - 3611A - 2004 Complaint Report of Double Thickness Tablet. See detailed analysis that follows
   - 70924A2 – Production Report of a Double Thickness Tablet. See detailed analysis that follows
   - 80202A1) – Bulk tablet lot was released[21] to filling and packaging only later to be placed on Hold due to tablet weight issues. "They indicated that this one is the problem child"[22]
   - 5453A – Tablet OOS for weight on the QA Over Check Data Sheet[23]
   - 80224A1 and 80227A1 – " is having an OOS issue with high weights, and these batches are suspect."[24] Note: these batches were finished and packaged and now QA was questioning the acceptability of the lots
   - 80228A1 – Investigation # 08-060 :"17 tablets with higher weight out of 30 tablets"[25], discovered in Packaging

2. Other Quality Problems with Digitek lots:
   - 70926A1 and 70953A1 "have Assays too low"[26]
   - 80044A1 – a stainless steel screw was found in tablet well during packaging (the compression process, which includes metal detection, did not detect the presence of a huge metal particle)
   - 80051A – Spots on tablets[27]
   - 80053A – Did not record metal detector and there is no record that the lot was reprocess through the metal detector
   - 70148A, and 70207A Digoxin Tablet 0.125 mg OOS[28] for blend uniformity
   - 70078A1 – Time zero (i.e. very beginning test) stability test results not recorded[29]
   - 70770A - OOS results for high RSD

[21] Exhibit #M-16 - Certificate of Conformance, Dan Bitler QA Director, dated 3/31/08
[22] Plaintiff's #143 – Re: Digitek batches on HOLD, Suzanna Wolfe, 4/2/2008
[23] Exhibit Plaintiff's #133 – Scott Talbot, Email Subject: Status Report – September 27, 2007, 9/27/2007
[24] Exhibit #143– Suzanna Wolfe, Email Subject: Digitek Batches On Hold, 4/2/2008
[25] Exhibit Plaintiff's 141 – Investigation # 08-060, No Author, No Date
[26] Exhibit # M-14 – Suzanna Wolfe, Email Subject: Digitek parameter review, 1/4/2008
[27] ACTAV 001868986 – 2008 Riverview Investigations, No author, No Date
[28] ACTAV 001869221 - Annual Product Review for 0.125 Digoxin Tablets, 3/17/08
[29] ACTAV 001580762 – Open Investigation Report – No Author, No Date, 4/30/2008 or more recent

- 70207A – Blend failure that was "Released"[30]
- 80108A –QA inspector verified wrong incorrect bar code[31]
- 800152A and 080154A – Process Validation protocol issues
- 70736A - OOS[32] for STR for Content Uniformity
- 70080A, 7081A, 70082A – High Impurity Level[33] – These batches were released. "All of them showed the high impurity result for Digoxigenin. It should have been a STR investigation and nobody did nothing (anything)"
- 80133A – Operator noticed that tablets were thinner during a routine inspection of a finished drum

These total 24 lots (seven (7) of which were OOS for thickness and/or overweight) of Digoxin with Quality problems, including OOS. Some of the lots were released, including OOS lots. This is an extraordinarily high incidence of significant problems, most of which are within a two (2) year period. This is especially concerning because Analyst records show that Digoxin is one of the "top 3 products in term of number of Adverse Event Reports where product was associated with a death or permanent injury outcome Digoxin 0.25mg[34]

3. 2007 Lab OOS - There were over 100 reported OOS within the QC Laboratory for 2007. A total of three (3) were specifically for Digoxin. *QC Laboratory 2007 OOS (Log) (Document 3006414)*[35]
4. 2008 Lab OOS - There were over 100 reported OOS within the QC Laboratory for 2008. A total two (2) were specifically for Digoxin. There was no apparent improvement when compared to the prior year. *QC Laboratory 2008 OOS (Log) (Document 3006420)*[36]
5. 2007 Investigations - There were over 100 Nonconformances that required a formal documented investigation. *Investigation Log 2007*[37]
6. 2008 Investigations - There were over 224 reported Nonconformance that required a formal documented investigation in *Investigation Log 2008*[38]. A total of ten (10) were specifically for Digoxin. There was well over a 100% increase compared to the prior year. Based upon this significant increase, GMP Compliance appeared to be progressively deteriorating.
7. 2008 Open Investigations(7 month period)[39] - There were 94 open product investigations for serious issues, the vast majority for product OOS
8. 2008 – 2009 (12 month period) Deviations - There is a 59 pages summary report that lists the unplanned *Deviations List Report* [40]that were conducted from 12/5/08 – 11/10/09 (12 month

[30] Exhibit 183 – Wanda Eng. Email Subject: Blend Failure locations, 7/20/2007
[31] ACTAV 001868986 – 2008 Riverview Investigations, No author, No Date
[32] ACTAV 001869221 - Annual Product Review for 0.125 Digoxin Tablets, 3/17/08
[33] Exhibit 172 – Email Subject :RE: Please explain, Jisheng Zhu, 3/19/2008
[34] Exhibit Plaintiff's #249 – Sarita Thapar, Email Subject: FW. Insurance Questions, 10/1/2007
[35] Document 3006414 – QC Laboratory 2007 OOS (Log)
[36] Document 3006420 – QC Laboratory 2008 OOS (Log)
[37] Document 3005608 – Investigation Log 2007
[38] Document 3005503 – Investigation Log 2008
[39] Document ACTAV 001580756 – Open Investigations (9/2007 – 3/2008)

period). There were a total of 247 unplanned deviations. At Actavis unplanned deviations are initiated when a batch/material/procedure is nonconforming/OOS and management determines if they wish to accept the nonconformance/OOS and continue to process the product, ultimately for release to the market place

9. 2006 – 2007 Rejections (17 month period) – According to *Rejected Batches from August 2006 through 2007 (17 months)*[41] there were approximately 20 batches rejected. This number is alarming, but not unexpected due to the high number of OOS, Deviations, and nonconformances over the same period of time. The greater issue is not the number of rejected batches (since these were caught) but the potential that other batches (that should have been rejected) were released for sale.
10. 2007 – 2008 OOS (8 month period) - There were a total of 96 OOS results that were recorded during the period of 9/07 – 4/08, according to an investigation report issued April 15, 2008[42]. This is an extraordinary number of OOS. During this eight (8) month period a total of nine (9) OOS involving 14 Digoxin lots. The OOS results were in multiple manufacturing and control areas.
11. Blending OOS - There were a total of 19 lots with product blending OOS[43]. As a result of the investigation, 6 lots were rejected, 6 were released for sale and 8 were still on hold (as of 7/20/2007). This number of blending nonconformances should have triggered a systematic review of the blending processes and then questions whether or not the processes are adequately validated. It should be noted that two (2) of the lots are Digoxin. One was released for sale. By contrast, most pharmaceutical operations have few if any blending OOS; however, if they occur, a comprehensive investigation and CAPA is implemented. These batches are usually destroyed because the OOS invalidates the process validation work done previously.
12. Investigation Review Board – Open Deviation Report [44] – On March 23, 2008 there were 53 open investigations into OOS. A total of 28 investigations into OOS were open for more than 50 days. Many were open for more than 100 days. The number of investigations is concerning; however; their length open is more concerning. Investigations of OOS must be completed quickly for several reasons. The longer the wait, the less probability that the root cause can be determined. Even more important is that this lengthy investigation has the potential to impact a much greater scope (than the specific batch of raw material or product). For example, if the OOS investigation determines that a commonly used instrument or test method does not provide accurate results, then the effects of this problem must be determined. If an investigation is done at day 100, then all of the tests conducted using this instrument and test method are suspect. The investigation into this type of event would be difficult with potentially widespread implications. Another example is process water used in product. If there was an OOS with water quality and the investigation was not conducted until 100 days later it must be determined the effect the OOS has on all product made since the OOS. Water is used in most

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[40] Document 3005547 – Deviation List Report (Log)
[41] Document 5475428 – Rejected Batches from August 2006 through 2007
[42] Exhibit Plaintiff's #217 – Mishbah Sherwani, Email Subject: FW: List by Product, 4/15/2008
[43] Exhibit 183 – Wanda Eng, Email Subject: Blend Failure locations, 7/20/2007
[44] Exhibit Plaintiff's #216 – Michael Ponzo, Email Subject: FW: Investigation Review Board Meeting *Rescheduled* UPDATE*, 3/28/2008

drug products. How do you investigate all of the products manufactured since the start of the OOS?

13. Ineffective Stability Testing Program

In the FDA documentation and correspondence, there were numerous products that failed the Stability Testing. Additionally, there were numerous mistakes associated with the testing.

It is important to understand that Stability Testing and subsequent analysis of the data, is the primary method to determine the shelf life (i.e. expiration date). Ongoing Stability Testing of marketed products is the primary method to verify that the product's labeled shelf life is correct. When a product tests OOS then the entire product in the market is suspect until an investigation is complete. After the investigation, it will be determined what the range of the issue is. When there is a breakdown of the Stability Testing Program, the quality of the product in the marketplace might not be assured.

14. Process Validation

"Approximately 25% of the commercial manufacturing equipment has not been qualified."[45] Process validation provides evidence that each product (bulk, tablets and packaging) conform to requirements and that sampling (such as in Stability Testing) is a valid method to determine the quality of all digoxin products. Since it was determined that many of the processes were not adequately validated, this further exacerbates the overall concerns and establishment of shelf life.

15. Product Recalls

The nonconforming product was of sufficient risk to the public to warrant the recall of all Digoxin products in the market. The reason for the recall is summed up in the following: "She stated that the reason the recall was expanded to all Digitek was that FDA felt that there weren't adequate controls on their tablet presses to assure that the double-thick tablet issue couldn't have happened previously"[46]

16. Mitigating Actions

In reading hundreds of Actavis documents, there is no mention to the implementation of immediate actions to mitigate the current risk. Within the drug industry, this is a highly common action when nonconformance occurs; especially, when the nonconformance is identified at a later stage of processing. For example, if a double thick tablet is found at packaging, it would be reasonable to assume that it was not picked up by the controls that were in place at compression (tablet making). There should have been consideration to having temporary inspections conducted at greater frequency by the operator and QA inspector (at compression and packaging). Although this type of mitigating action will not eliminate the source of the nonconformance, it will increase the probability of detecting the defect. This type

[45] MLYN 000032279 - FDA 483 for Little Falls NJ - Issued by the Parsippany NJ office, 12/1/04

[46] Exhibit #M-5, Email Subject: Actavis (Amide) Recall and FDA Inspection, Chuck Koon (Vice President of Quality Assurance at Mylan), 4/27/2008

of action is short term but may help reduce the risk but it will not eliminate defects. Likewise, there was no mention to investigating automatic weighing to potentially detect each defect. Early detection will greatly increase the probability of finding the root cause of the nonconformance.

Quality & Quality Systems
SpyGlass Group Summary

It is my opinion to a reasonable degree of certainty that Actavis failed to establish reliable and GMP compliant systems and procedures resulting in the release of adulterated product from at least the period of 2004 – 2008.

c. Double Thick Complaint Lot 3611A

Double Thick Digoxin Tablets 0.25 mg – Lot 3611A

2007 Investigation No: 04-003 – Complaint Investigation

FINDINGS

Investigation Report 04-003[47] summarizes the results from a customer complaint received by Actavis on 7/7/04. A pharmacist returned a 0.25 mg Digoxin tablet from Batch # 3611A which was approximately twice normal thickness and weighed twice as much. Two Stokes compression machines were used on Batch # 3611A. Under normal operation these machines cannot make double thickness tablets. Upon machine set up however, double thickness tablets can be made. In this case double thickness tablets are observed by the set up operator who adjusts the machine and thinks he/she cleared the area of any double thickness tablets prior to actual production startup. QA's inspection did not detect the defect. The compression operation begins and lasts for several days until the bulk blended batch is exhausted. There are several long interruptions in the tableting process; the most significant is a stop for cleaning where the punches are removed and the equipment is then readjusted. QA then occasionally monitors the quality of the product and conformance to procedures. The batch size target is about 4.8 million tablets and a single batch of digoxin tablets can take several days to compress.

Investigation 04-003 concluded the most probable cause of double thick tablets was that they were made during the initial setup, the single tablet returned became stuck in the deduster and was not removed or detected prior to starting the production run.

The following identifies some of the serious issues with the actions and documentation associated with Complaint Investigation Report 04-003

- Approval by Top Management: - The Investigation Report is not signed and dated. The Investigation Final Report was never approved by Senior Management as required by the SOP. The SOP requires the following management approvals:
    - Quality Assurance Director
    - Vice President Scientific Affairs
    - Manufacturing Operations Director

  This is a violation of cGMP. An undated and unapproved/unsigned document does not provide formal/legitimate evidence that the right things were done.
- Corrective Action Dates – There are no dates associated with the corrective action
- Analysis of the Complaint Sample: There was no analytical testing of the complaint sample

[47] Exhibit Plaintiff's #128 – Amide Pharmaceutical, Inc. Investigation Final Report No. 04-003, Initiated 7/9/04

- Critical Corrective Action - The investigation documents do not list the procedures, etc. that were corrected. The document should not have been approved unless there was specific reference to the document(s) that were corrected. There should also have been a documented verification on the effectiveness of these changes.
- Undisciplined & Inadequate Investigation – The investigation does not follow any generally accepted problem solving approach or method. The root cause was never identified, yet the investigation only focused on cleaning the deduster and chutes at start-up. There are many more potential root causes that were not considered.
- Inadequate Investigation and Corrective Action – The corrective action was not effective as was evidenced by a repeat double thick tablet incident (Lot 709241A1/A2)

DOUBLE THICK COMPLAINT LOT 3611A
SPYGLASS GROUP SUMMARY

It is my opinion based upon a reasonable degree of certainty that Actavis demonstrated general inability to handle this critical product quality crisis. Had the proper investigation been performed, a root cause would have been determined and the weak links in their practices might have permanently resolved the double thickness matter. In 2004 Actavis released product with serious defects. Actavis' response to this serious issue was not adequate and the actions did not comply with the GMP Regulations. The complaint samples might have been double or more of the labeled dosage. Based upon the lack of GMP controls in place at the plant, there is no reason to believe that this was an isolated incident. There was inadequate investigation; therefore, the problem was likely to resurface. The same problem did resurface in 2007.

d. Lot 70924 2nd Report of Double Thickness Tablets

Report of Double Thickness Digoxin Tablets 0.125 mg - (Lot #70924A1/A2)

2007 Investigation Log # 70-093[48]

FINDINGS

The chronology of the events associated with the double thick Digitek tablets is as follows:

The double thickness Digitek problem surfaced again on 11/30/2007 when five (5) double thick tablets were discovered while in the middle of packaging the lot. It is important to note that the double thick tablets were never detected at tableting. Packaging continued with the QA instructions "If one or two thick tablets found, continue packaging operation with a watchful eye."[49] This clearly was inadequate direction. During the packaging a total of 15 additional double thick tablets were found in drums 15/16, 17 and 34. On 12/04/2007 this packaged batch was released for sale. On 12/05/2007 this batch was placed on hold by QA. On 1/11/2008 the batch was salvaged by 100% visual inspection. On 1/22/2008 the lot was sampled by QA, no additional tablets were found. On 1/23/2008 the inspected batch was approved for packaging. On 1/28/2008 the batch was approved by QA. See the *Appendix C – Chronology of Lot 70924 – Double Thick Lot.*

FDA issued a 483[50] on an inspection of 993 Riverview Drive from an inspection from 3/18/08 to 5/20/08 with 11 major observations. Observation 2 states that "Drugs products fail to meet established specifications and quality control criteria are not rejected." Specifically it states in 2a. "During packaging of Digoxin Tablets 0.125 mg, lot #70924A1, five double thick tablets were observed. Quality Assurance approved a 100% visual inspection of the 4.8 million tablet lot which resulted in an additional 15 double thick tablets. Although Quality Assurance was aware of the "double thick' tablet findings, the batch was then released based on AQL sampling which included visual inspection of 1330 tablets. No root cause was determined for the defect; however the lot was released to the market by the Quality Unit on 1/28/08 following the visual inspection. There was no documented evaluation of the approximately 89 lots remaining on the market at the time of inspection." The FDA had grave concerns about all 89 lots that were released for sale to the public. The facts of this situation ended with a mandate for full product recall.

There are many issues associated with the handling of the double thickness issue.

[48] Plaintiff's Exhibit #16 – Investigation Report #07-093, Batch #70924, 12/5/2007
[49] Incident Report; from Packaging Manager and Supervisor, 12/1/2007
[50] Plaintiff's Exhibit #91 – FDA EIR, inspection of 8/18 to 5/20/2008

Unexplained Decisions

- When the defective tablets were later discovered in packaging, the packaging operation was allowed to continue. The operation should have been immediately halted. All products made to that point should have been immediately placed on hold and properly labeled as such. There should have been no further processing until a comprehensive investigation was conducted.
- On 12/4/2007 uninspected finished product lot containing defects was released for sale by Quality Assurance. A day later (12/05/2007), QA reversed their decision and decided that the batch was not acceptable and should not be distributed. How could an event like this occur in a well controlled environment? This is a breakdown of the highest order. The distribution of the lot was halted and the product lot was placed back on hold without any documented reason for this action. This incident alone should have been classified as a serious high priority nonconformance and properly investigated, including a potential CAPA. The batch was subsequently salvaged by breaking down the package, saving the tablets, visually inspecting the lot to eliminate defects, repackaging and then re-releasing the salvaged batch. The justification for these actions was not documented.

Inadequate Quality Problem Investigation

- Root cause of the problem was never confirmed but "appeared" to be caused at compression machine startup.
- Tablet compression was on 2 Stokes Presses over a 3 day period. The presses were stopped a total of 18 times for breaks, lunch, and overnight with very few QA checks on restart. Stoppages ranged from 20 minutes to 17 hours.
- Actavis identified the lack of cleaning of the deduster at compression startup as a potential root cause; however, records indicate that this may not be correct. A total of 20 double thick tablets were found in the batch. Their Investigation 07-093[51] determined that the only opportunity for this to occur was at compression startup. This conclusion may be flawed. Five (5) tablets were found in the first inspection process in buckets #15 &#16 (2 tablets within both buckets), #17(1 tablet), and #34(2 tablets) and in 100% inspection another 15 with no locations noted. This indicates that the problem occurred throughout tableting or original filling process and not just at startup. This information was never even considered during the root cause analysis. Again, how could these all be the result of startup when they were spread throughout many buckets?
- Investigation is incomplete and never included other potential root causes to the production of double thick tablets, including:
    - There is no documented investigation into complaint history for similarly manufactured tablets, including other tablet product made by the same or similar process and equipment
    - Double thick tablets were never chemically tested. The dose of the double tablets is not known.
    - No review of records to determine if the equipment is qualified and the process validated
    - No review of the training records of the associates

[51] ACTAV 000002766 – Memo Subject Investigation 07-093, Michael Manzo, 1/8/08

- No consideration of design changes to the equipment to eliminate future defects
- No review of the proper use of defect buckets and labeling practices
- No detailed review of the history of this type of nonconformance
- No clear conclusions resulting from the investigation
- No investigation into the history of changes to the equipment
- No review of the preventive maintenance of the tableting equipment
- No inspection of the other lots of Digoxin tablets within their control or on the market

- There was no subsequent increase in QC checks or other controls (intended to add further probability to detect double thickness tablets). Some steps should have been implemented to mitigate the risk since the root cause of the problem was never determined.
- Unexplained Increase in Quantity after Packaging - The records show that the repackaged batch had an increase in the quantity after 100% inspection and repackaging. An unsigned and undated memo[52] from Ashesh Dave attempts to explain the discrepancy. The investigation was not extensive merely focusing on weigh errors.

Ineffective and Unreliable Methods to Salvage a Known Defective Tablet Batch

- Production and Quality Assurance used a method to salvage a defective batch (containing double thick tablets) that is generally not accepted in the drug industry as being effective, i.e. their method for attempting to cull out 100% of the defects within a 4,800,000 tablet batch through human 100% visual inspection. This method of visually inspecting out defects is known throughout the medical products' industry to be unreliable. It is one of the more famous quotes that 100% inspection is no better than 80% effective. Said another way, 100% Inspection is not 100% effective. Based upon this industry's accepted understanding, it is almost certain that further defective tablets remained in the batch. (Ref. Juran[53] and Craig QP 2004 July[54])

- After 100% inspection, the batch was subjected to another QA inspection using a tightened AQL where each of the 34 individual buckets from the batch was randomly sampled[55] with 40 tablets each. After visual inspection, a Quality Control sample inspection was designed to allow less than 100% effectiveness. The batch could be released even if a defect was found in the final QA samples (i.e. the lot would pass if one (1) defective tablet was found in the samples, only rejecting if two (2) or more defective tablets were found.) The "tightened "AQL testing plan would have released the batch even if one defective tablet was found. What was QA and Management thinking?

- There is no documented procedure that describes the equipment, techniques and methods used in the 100% visual inspection.
- There was no Quality Assurance monitoring of the visual inspection.

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[52] Disposition Exhibit -#168 – Subject: An explanation for two additional bottles in the final yield after repackaging of the batch, Not Date

[53]Quality Control Handbook, J.M.Juran, 3rd Ed. , 1951, McGraw-Hill, pp. 12-61 to 12-63. On 100% Inspection Accuracy

[54] , Quality Progress, D.J.Craig, July 2004. On 100 % Inspection Accuracy.

[55] Sampling Plan - The sample and test plan was as follows: AQL level = 0.065, Sample Plan= single, tightened level 1, Sample Size Code = Q, Bulk Size ~ 4.8 million, Inspect 1250 tablets minimum from 34 drums. 40 from each of 33 drums, 10 from 34th drum. Tablets taken at random, Accept on 1/reject on 2 of total batch

- There is no documentation that the inspectors were properly trained on the inspection method
- The salvage method was not properly approved. There was no approved Deviation Record to authorize the procedure of tearing down finished product and 100% inspecting.
- There is no record that the visual inspection procedure is effective. The procedure was never qualified. How thick does a tablet have to be identified in a 4.8 million tablet lot?
- The acceptance criteria for 100% inspection not established. How thick was too thick?

Inadequate Batch Record Detail of the Lot Salvaged Through 100% Inspection

- There is no documented evidence that the defective lot was properly salvaged. For example, the following required information was not included in the batch record:
  - Inspection Start and End Date/Time
  - Name and document number of the 100% inspection procedure/method
  - Startup inspection
  - Clean up inspection
  - In-process Quality inspection monitoring
  - Inspector's names
  - Inspector's training records
  - Deviation authorization number
- The inspection protocol did not include the required information, for example:
  - Inspection Procedure
    - What is the Quality Standard
    - Were the tablets spread out on a tray?
    - Did they have increased light or other enhancements for visual improvement?
    - Did they need to wear gloves?
    - How did they transfer the tablets?
    - How did they segregate the double thick tablets?
    - What if other defects are discovered (black spots, broken, discolored)? Are these noted in the records? How will it be handled?
  - Acceptance Criteria and Specifications
  - Responsibilities
- The activities were handled according to incomplete and disjointed memos and apparent verbal instructions.

LOT 70924 2ND REPORT OF DOUBLE THICKNESS TABLETS

SPYGLASS GROUP SUMMARY

- Batch # 70924 should have been rejected and destroyed. There is no confidence that the process was capable of producing defect free tablets. The methods and procedures in place during the production of Lot 709241A were not in compliance to FDA GMP Regulations. It is not possible to defend management's action in this regard.
- Significant violations of GMP contributed to the production of a lot containing critical defects, i.e. "double thick tablets".
- After the discovery of tablet defects, the lot was not destroyed. In fact, there appeared to be continuous waffling back and forth in terms of the correct disposition of the batch.
- In the attempt to salvage 4,700,000 tablets, the defective batch was further processed using ineffective and unvalidated methods that would not have provided a high level of assurance that the lot was defect-free. Among the unvalidated methods, a human 100% inspection process is not effective and will not remove all defective tablets, especially in such a large batch. Can you visualize operators looking at millions of tablets? It was in some ways like trying to find a needle in a haystack.
- Because the investigation was inadequate, the corrective action may not be effective in preventing recurrence of the double thick tablets.
- I challenge the wisdom in the decision to release Digitek, digoxin 0.125 mg, Batch # 70924 for sale. I challenge the decision not to reject and destroy the batch. As with many other nonconformance, deviations and OOS, a root cause determination was not evident and the corrective action to prevent recurrence was either not effective or never implemented. An experienced Quality Assurance Head would not have followed the Actavis decision making path.

e. FDA Observations & Other Events

The Federal Government cited Actavis for serious GMP violations in at least 6 FDA inspections over a period of 2004 to 2008 issuing a Permanent Injunction on 11/12/08. This injunction shut down the plant.

FDA records demonstrate that there were unacceptable and noncompliant practices for a six (6) year period. An analysis of the FDA 483's, Warning Letters and Permanent Injunction confirm that there were repeated nonconformances in the fundamental control systems; including,

- Quality System
- Facilities & Equipment System
- Production System
- Laboratory System
- Regulatory Requirements

The observations are summarized in *Appendix F – FDA Observations & Events.* A review of this document will confirm the pattern of repeat nonconformance.

The following summarizes some of the system issues identified by the FDA.

Quality System

The FDA identified Quality System issues in every 483 report. The observations included:

- Changes made to records without approvals
- Inadequate investigations of complaints
- Inadequate investigation of nonconformances
- Failure to prevent the release of lots with significant nonconformances
- Batch failures not investigated

Facilities & Equipment System

- 25% of the manufacturing equipment is not qualified
- Inadequate preventive maintenance program
- Equipment qualification issues

Production System

- Lack of Cleaning Validation
- Production documentation not controlled to protect unauthorized changes
- Inadequate inprocess testing
- Deviations from production and process control

- Records not complete
- Inadequate storage practices
- Procedures not followed

Laboratory System

- Stability Testing Protocol not followed
- Unsecure computer records
- Quality testing records incomplete
- Changes to lab notebooks after it was approved
- Original OOS results not recorded
- Lab computer system is not validated
- Examples where products did not meet specification throughout the product's shelf life
- Lab controls that are not scientifically sound

Regulatory Requirements

- Adverse Drug Experience (ADE) information not reported to the FDA
- ADE not investigated
- Procedures not established for post marketing ADE
- Field Alert Reports not submitted on time

SPYGLASS GROUP SUMMARY

Over the 2004 – 2008 time periods, all products made at Actavis were in violation of GMP and are therefore adulterated.

The root cause of complaint and product issue is invariably linked to GMP nonconformance. The lack of an effective Quality System creates and unacceptable Product Quality & Regulatory Compliance risk.

This repeat pattern of serious violations to GMP, the release of nonconforming product and the FDA's intolerance to the continuation of this unacceptable public risk, resulted in a court ordered closure of the plant.

There was a general lack of well-established Quality Systems. The importance of a well established Quality Systems cannot be overstated. My experience is that the lack of a Quality System creates an environment where defective products can be produced and subsequently released to the market.

f. Recall.

A review of Appendix *F – Summary of FDA Observations and Events* will confirm that serious violations occurred, including the release of Digoxin that failed to meet established standards and specification and other relevant quality control criteria. As a result of the FDA concerns, a complete recall of all Digitek lots was conducted. See *Appendix D Press Release – Digitek Product Recall 25-APR-2008.*

A review of Appendix *F – Summary of FDA Observations and Events* will confirm that serious violations occurred, including the release of many products that failed to meet established standards and specification and other relevant quality control criteria. As a result of the FDA concerns, a recall of 66 different products was conducted. See Appendix *E – Press Release – Products Manufactured at Little Falls)*

g. Mylan

Responsibilities (Quality Agreement)[56] – Mylan never established a written agreement between both companies that stated each other's responsibilities and the action steps for complying with the GMP regulations. On about 1/29/2007 Mylan attempted to establish responsibilities between each company which is years after starting their business together. It is difficult to understand that it took eight (8) years to realize that their mutual responsibilities and accountabilities had not been established.

Complaint Handling – Mylan is the company responsible for fielding customer complaints, including medical complaints. Mylan is then required by GMP to investigate all complaints. In the case of Digoxin, it would be expected that Mylan share the complaint information and then require Actavis to perform their investigation. This should be done in accordance to a mutually approved Quality Agreement. Actavis would then communicate their findings and if applicable corrective actions. There is no evidence to demonstrate that Mylan detected the lack of an adequate investigation and corrective action to the double thick complaint.

GMP Auditing of Digitek - The records demonstrate that one GMP audit[57] of Actavis was conducted by Mylan. This audit focused on Digoxin. Most drug companies audit their external manufacturers at a frequency of once every 1 – 2 year period unless there is documented justification to decrease the frequency. It does not appear that Mylan met this industry norm. There is no evidence that the audit was a systematic review of the required GMP control systems as is the norm in the industry. There is no evidence that the audit included a review of deviations, nonconformances, specifications, lab testing records and batch history records as is the norm in the industry. On the contrary, the audit appears to be a plant tour and an onsite update of Actavis' FDA related activities. There is no GMP audit agenda nor is there any indication that any section of the GMPs was audited.

It is my opinion to a reasonable degree of certainty and based upon reviewing the records of over two hundred drug and device companies (including dozens of contract manufacturers) that Mylan did not have in place the minimum control systems for qualifying and monitoring contract manufactures as required by

[56] Exhibit #M-23 – Document from Mylan, No name identified (Potentially P. Latzo), about 1/29/2007
[57] Exhibit # MYLN 000030 (number not clear) – R. Pinnell and P. Streater, Audit Number: XA-06-010, 12/04/06

GMP. Additionally, one audit within a 9+ year period is not adequate to ensure that companies producing Mylan's products fully meet GMP requirements.

It is my opinion to a reasonable degree of certainty, that if Mylan had conducted GMP audits (using a highly qualified GMP auditor or audit team) prior to awarding the contract and 1-2 years thereafter, then they would have detected the GMP issues prior to the FDA's series of inspections and subsequent escalation activities.

Expert Witness Final Summary

There were critical quality and Good Manufacturing issues identified at almost every point in the production, control and testing processes. There was a breakdown in their Quality Systems that allowed mistakes and errors in judgment to occur. Over at least a four (4) year period, Actavis released adulterated product, including Digoxin.

It is my opinion to a reasonable degree of certainty that the GMP Compliance and Quality problems might have been averted if early in the problem discovery phase, management had taken appropriate actions, including placing priority on the fixes. Based upon the records, they were constantly fighting ever increasing fires and continually being faced with nonconforming product and noncompliant practices. Faced with the responsibility of making high Quality products while trying to put out the fires eventually became an insurmountable task.

It is my experience that good people don't come to work with the intention of doing a bad job. It is the company's misguided values, principles and work-ethics (established by Actavis top management) that fostered bad behavior. The Actavis environment was not focused on GMP and Product Quality; therefore, all involved suffered the adverse consequences.

As quoted earlier "This is all rather sad. Looks like some very basic GMP knowledge was lacking."

Mark G. Kenny

Managing Director

SpyGlass Group, Inc.

6/15/2010

Date

Appendices

A. Mark G. Kenny CV
B. References
C. Chronology of lot 70924 – Double Thick Lot
D. Press Release – Digitek Product Recall 25-APR-08 (Recalled)
E. Press Release – Products Manufactured at Little Falls (Recalled)
F. Summary of FDA Observations and Events

Appendix B - References

1. Quality & Compliance Consulting Group – website: www.spyglassgroupinc.com
2. 21 CFR Part 210 and 21 CFR Part 211 Current Good Manufacturing Practice for Manufacturing, Processing, Packing, or Holding of Drugs and Finished Pharmaceuticals
3. FDA Form 483, Issued to Divya C. Patel (President), District FDA Office in Parsippany - NJ, 12/1/042004
4. Plaintiff's Exhibit #82, Complaint of Permanent Injunction, 11/14/08
5. Plaintiff's Exhibit #124 – Definition of an adulterated drug, US doc. 351.
6. Appendix D Summary of FDA Observations & Events
7. http://www.cgmp.com/warningLetter.htm
8. http://www.actavis.com/en/products/manufacturing/good+manufacturing+practice.htm
9. Plaintiff's Exhibit #147 – Email Subject: Form FDA 483 RV.pdf, Jacob Haroon, 5/27/ 2008
10. Complaint for Permanent Injunction, Case 2:08-cv-05656-SDW-MCA, Christopher Christie (United States Attorney), Filed 11/14/2008, p 11
11. Exhibit Plaintiff's #146- Email Subject: Totowa Potential 483 items and comments, Wanda Eng, 4/17/2008
12. Plaintiff's Exhibit 229 – Warning Letter, Douglass Ellsworth, August 15, 2006
13. Mylan Audit, Subject: Final Corrective Action Memo, from R. Pinnell, 1/23/2008
14. Exhibit Plaintiff's #137 – Totowa Action Plan (August 2006 GMP Inspection Totowa), Not dated - estimated July 2007
15. Plaintiff Exhibit #25 – Revised Warning Letter, 2/2007
16. Exhibit Plaintiff's #106 - Subject: FDA Little Falls Inspection Closeout – May 20, 2008, Garret R. Woolan – Scribe, 5/20/2008
17. ACTAV 000484606 – Quality System Improvement Plan, 2/26/2009
18. Plaintiff's #175: M. Patel, Email Subject: Regarding internal cGMP audit, 1/25/2008
19. Plaintiff Exhibit #25 – Revised Warning Letter, 2/2007
20. Exhibit Plaintiff's #92 – Presentation at a Feb 2006 Sales Meeting, Not Dated
21. Exhibit #M-16 - Certificate of Conformance, Dan Bitler QA Director, dated 3/31/08
22. Plaintiff's #143 – Re: Digitek batches on HOLD, Suzanna Wolfe, 4/2/2008
23. Exhibit Plaintiff's #133 – Scott Talbot, Email Subject: Status Report – September 27, 2007, 9/27/2007
24. Exhibit #143– Suzanna Wolfe, Email Subject: Digitek Batches On Hold, 4/2/2008
25. Exhibit Plaintiff's 141 – Investigation # 08-060, No Author, No Date
26. Exhibit # M-14 – Suzanna Wolfe, Email Subject: Digitek parameter review, 1/4/2008
27. ACTAV 001868986 – 2008 Riverview Investigations, No author, No Date
28. ACTAV 001869221 - Annual Product Review for 0.125 Digoxin Tablets, 3/17/08
29. ACTAV 001580762 – Open Investigation Report – No Author, No Date, 4/30/2008 or more recent
30. Exhibit 183 – Wanda Eng. Email Subject: Blend Failure locations, 7/20/2007
31. ACTAV 001868986 – 2008 Riverview Investigations, No author, No Date

32. ACTAV 001869221 - Annual Product Review for 0.125 Digoxin Tablets, 3/17/08
33. Exhibit 172 – Email Subject :RE: Please explain, Jisheng Zhu, 3/19/2008
34. Exhibit Plaintiff's #249 – Sarita Thapar, Email Subject: FW. Insurance Questions, 10/1/2007
35. Document 3006414 – QC Laboratory 2007 OOS (Log)
36. Document 3006420 – QC Laboratory 2008 OOS (Log)
37. Document 3005608 – Investigation Log 2007
38. Document 3005503 – Investigation Log 2008
39. Document ACTAV 001580756 – Open Investigations (9/2007 – 3/2008)
40. Document 3005547 – Deviation List Report (Log)
41. Document 5475428 – Rejected Batches from August 2006 through 2007
42. Exhibit Plaintiff's #217 – Mishbah Sherwani, Email Subject: FW: List by Product, 4/15/2008
43. Exhibit 183 – Wanda Eng, Email Subject: Blend Failure locations, 7/20/2007
44. Exhibit Plaintiff's #216 – Michael Ponzo, Email Subject: FW: Investigation Review Board Meeting *Rescheduled* UPDATE*, 3/28/2008
45. MLYN 000032279 - FDA 483 for Little Falls NJ - Issued by the Parsippany NJ office, 12/1/04
46. Exhibit #M-5, Email Subject: Actavis (Amide) Recall and FDA Inspection, Chuck Koon (Vice President of Quality Assurance at Mylan), 4/27/2008
47. Exhibit Plaintiff's #128 – Amide Pharmaceutical, Inc. Investigation Final Report No. 04-003, Initiated 7/9/04
48. Plaintiff's Exhibit #16 – Investigation Report #07-093, Batch #70924, 12/5/2007
49. Incident Report; from Packaging Manager and Supervisor, 12/1/2007
50. Plaintiff's Exhibit #91 – FDA EIR, inspection of 8/18 to 5/20/2008
51. ACTAV 000002766 – Memo Subject Investigation 07-093, Michael Manzo, 1/8/08
52. Disposition Exhibit -#168 – Subject: An explanation for two additional bottles in the final yield after repackaging of the batch, Not Date
53. Quality Control Handbook, J. M. Juran, 3rd Ed., 1951, McGraw-Hill, pp. 12-61 to 12-63. On 100% Inspection Accuracy
54. Quality Progress, D. J. Craig, July 2004. On 100 % Inspection Accuracy.
55. Sampling Plan - The sample and test plan was as follows: AQL level = 0.065, Sample Plan= single, tightened level 1, Sample Size Code = Q, Bulk Size ~ 4.8 million, Inspect 1250 tablets minimum from 34 drums. 40 from each of 33 drums, 10 from 34th drum. Tablets taken at random, Accept on 1/reject on 2 of total batch
56. Exhibit #M-23 – Document from Mylan, No name identified (Potentially P. Latzo), about 1/29/2007
57. Exhibit # MYLN 000030 (number not clear) – R. Pinnell and P. Streater, Audit Number: XA-06-010, 12/04/06
58. Deposition of Chuck Koon – Dated 5/21/2010, No exhibit number
59. http://www.actavis.us/en/media+center/newsroom/articles/digitek+recall.htm
60. http://www.actavis.us/en/media+center/newsroom/articles/Actavis+Totowa+Recall.htm

Appendix C – Chronology of Lot 70924 – Double Thick Lot

Date	Action
11/12/2007	Digitek Lot Number 70924A was started – Theoretical batch size of 4,800,000
11/16/2007	Tablet Compression Machine was set up
11/17/2007	Started Compression (one operator was running 2 tableting lines)
11/18/2007	Finished Containers 1 – 14
11/19/2007	Stopped, removed and cleaned upper and lower punches due to excessive build-up of powder (press 67)
11/19/2007	Finished Containers 15 – 26
11/20/2007	Finished Containers 27 – 34 (final container)
11/29/2007	Packaged 4,754,000 million tablets
11/30/2007	Two tablets found on line #405. Two prior buckets inspected with no additional double thick. Packaging resumes. QA instructed "If one or two thick tablets found, continue packaging operation with a watchful eye". A total of 5 double thick tablets were found. (buckets 15/16, 17 and 34)
12/01/2007	Competed, found "only" one tablet from Bucket # 17
12/01/2007	Finished stock transfer sheet completed to move product into accepted status
12/04/2007	Finished product approved and formally released by QA
12/05/2007	Batch placed on hold
1/11/2008	Bitler issues Inspection Protocol authorizing 4,722,000 tablets to be inspected
1/18/2008	Repackaged batch passed the reinspection requirements (a total of 15 double thick tablets were found during 100% inspection)
1/21/2008	QA Sample Inspection protocol issued
1/22/2008	QA Sample Inspection completed – no double thick tablets found in sample
1/23/2008	Ashesh Dave issues email stating that the line operator found thick tablets previously at packaging and is requesting to repackage the lot
1/23/2008	Finished product acceptable
1/24/2008	Packaged 4,754,000 salvaged tablets
1/24/2008	Ponzo issues an investigation summary
1/25/2008	Batch accepted/authorized for repackaging (Dan Bitler approved) AFTER repackaging
1/28/2008	Lab results indicate acceptable
1/28/2008	Batch released
1/30/2008	Batch shipped

Appendix D – Press Release – Digitek Product Recall 25 APR 2008

Actavis Press Release[58]

Actavis Totowa (formerly known as Amide Pharmaceutical, Inc.) recalls all lots of Bertek and UDL Laboratories Digitek (digoxin tablets, USP) as a precaution

Morristown, NJ, 25 April, 2008 - Actavis Totowa LLC, a United States manufacturing division of the international generic pharmaceutical company Actavis Group, is initiating a Class 1 nationwide recall of Digitek (digoxin tablets, USP, all strengths) for oral use. The products are distributed by Mylan Pharmaceuticals, Inc. under a "Bertek" label and by UDL Laboratories, Inc. under a "UDL" label.

The voluntary all-lot recall is due to the possibility that tablets with double the appropriate thickness may have been commercially released. These tablets may contain twice the approved level of active ingredient than is appropriate.

Digitek is used to treat heart failure and abnormal heart rhythms. The existence of double-strength tablets poses a risk of digitalis toxicity in patients with renal failure. Digitalis toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can also result from excessive Digitalis intake. Several reports of illness and injuries have been received.

Actavis manufactures the products for Mylan and the products are distributed by Mylan and UDL under the Bertek and UDL labels. Bertek and UDL are affiliates of Mylan.

Any customer inquiries related to this action should be addressed to Stericycle customer service at 1-888-276-6166 with representatives' available Monday through Friday, 8 am to 5 pm EST. Additional information about the voluntary recall can also be found at www.actavis.us.

Retailers who have this product are urged to return the product to their place of purchase. If consumers have medical questions, they should contact their health care providers.

This recall is being conducted with the knowledge of the Food and Drug Administration.

Any adverse reactions experienced with the use of this product, and/or quality problems should also be reported to the FDA's MedWatch Program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, by mail at MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or on the MedWatch website at www.fda.gov/medwatch.

[58] http://www.actavis.us/en/media+center/newsroom/articles/digitek+recall.htm

Appendix E Press Release - Products Manufactured at Little Falls

Actavis Press Release[59]

02 AUG 2008 / Product

Actavis Totowa Announces Voluntary Recall at the Retail Level of All Drug Products Manufactured at its Little Falls, New Jersey Facility

Morristown, NJ, 1 August, 2008 — Actavis Totowa LLC, a generic drug manufacturer, is announcing a voluntary recall, to the retail level, of all drug products manufactured at its Little Falls, New Jersey facility. This is a precautionary, voluntary action by Actavis following an inspection conducted by the Food and Drug Administration earlier this year.

The inspection at Little Falls revealed operations which did not meet the FDA's or Actavis' standards for good manufacturing practices. Actavis Totowa is voluntarily recalling these products from the pharmacy/retail level, which includes wholesalers and hospitals. The company has informed the FDA regarding this action.

This action is not prompted by product complaints or health hazards associated with the products, which are all prescription medications. Patients who may have these medicines in their possession should continue to take them in accordance with their prescriptions, as the risk of suddenly stopping needed medication may place patients at risk. If patients should wish to obtain replacement medications and/or prescription, they should contact their health care professional or pharmacist. For more information regarding this market action, please visit

http://www.actavis.us/en/media+center/newsroom/articles/RecallFAQ.htm

Recall letters have been issued to wholesalers and retailers, instructing them to return product to Capital Returns, Milwaukee, WI.

Actavis Totowa, LLC is a United States subsidiary of Actavis Group hf. This voluntary action is limited only to the Actavis Totowa products manufactured in the Little Falls, NJ facility listed below. Products manufactured by Actavis Elizabeth LLC, Actavis South Atlantic LLC, Actavis Mid Atlantic LLC or Actavis products manufactured in other facilities are thus not impacted by this recall

The recalled products manufactured at the Little Falls facility are:

Amantadine 100mg capsules	Meperidine & Promethazine capsules
Amibid DM ER tablets	Meperidine HCl 100 mg and 50 mg tablets
Amibid DM tablets	Methenamine Mandelate 0.5 g and 1.0 g tablets
Amidrine capsules	Mirtazapine 15 mg, 30 mg, and 45 mg tablets

[59] http://www.actavis.us/en/media+center/newsroom/articles/Actavis+Totowa+Recall.htm

Amigesic 500 mg caplets and 750 mg caplets	Mirtazapine OD tablets, 15 mg, 30 mg and 45 mg
Amitex PSE tablets	Multi-ret Folic 500 mg tablets
Bellamine S tablets	Multi-vita-bets 0.5 mg and 1.0 mg FL & FE tablets
Betaxolol 10 mg and 20 mg tablets USP	Multi-vita-bets 0.25 mg, 0.5 mg and 1 mg FL tablets
Buspirone HCL 5 mg, 10 mg, 15 mg and 30mg tablets	Naltrexone 50mg tablets
Carisoprodol & Aspirin tablets	Oxycodone & Acetaminophen 5/500mg capsules
Carisoprodol, Aspirin & Codeine tablets	Oxycodone HCl 5 mg, 15 mg and 30 mg tablets
Carisoprodol 350mg tablets	Oxycodone HCl 5 mg capsules
Chlordiazepoxide w/ Clidinium Bromide capsules	Pentazocine & Acetaminophen tablets
Chlorzoxazone 250mg	Pentazocine & Naloxone tablets
Cilostazol tablets 100mg	Phenazopyridine HCl 100 mg and 200 mg tablets
Choline Magnesium Trisalicylate 500 mg, 750 mg and 1000 mg tablets	Phendimetrazine Tartrate 35mg tablets
Cyclobenzaprine HCL 5 mg and 10 mg	Phentermine HCl 37.5 mg tablets
Dexchlorpheniramine Maleate 4 mg and 6 mg tablets	Phentermine HCl 15 mg, 30 mg and 37.5 mg capsules
Dipyridamole 25 mg, 50mg, and 75 mg tablets	Prenatal Formula 3 tablets
Glyburide 1.5 mg, 3.0 mg and 6.0 mg tablets	Prenatal Plus 27 mg FE tablets
Guaifenesin & Codeine Phosphate tablets	Prenatal Rx tablets
Guaifenesin & Phenylephrine tablets	Quinaretic 10mg/12.5mg, 20 mg/12.5 mg and 20 mg/25 mg tablets
Guanfacine 1.0 mg and 2.0 mg HCl tablets	Rifampin 300mg capsules
Hydrocodone & Homatropine tablets	Sodium FL 0.5 mg and 1.0 mg tablets
Hydromorphone HCl tablets	Tizanidine HCl 2 mg and 4 mg tablets
Hydroxyzine 10 mg, 25 mg and 50 mg tablets	Trimethobenzamide 300mg capsules
Hyoscyamine Sulfate 0.125 mg SL	Trimipramine Maleate 25mg, 50mg, 100mg capsules
Hyoscyamine Sulfate 0.375mg SR tablets	Trivita 1 mg FL tablets
Hyoscyamine Sulfate 0.125 mg (oral) tablets	Ursodiol capsules, 300mg
Isradipine 2.5 mg and 5 mg capsules	Vitacon Forte capsules
Loxapine 5 mg, 10 mg, 25 mg, and 50 mg capsules	Vitaplex Plus tablets
Meclizine Chewable 25 mg tablets	Vitaplex tablets (FC)
Meloxicam 7.5 mg and 15 mg tablets	Yohimbine HCl 5.4 mg tablets

Appendix F – Summary of FDA Observations and Events

EVENT & LOCATION	QUALITY SYSTEM	FACILITIES & EQUIPMENT - SYSTEM	PRODUCTION SYSTEM	LABORATORY & CONTROL SYSTEM	REGULATORY REQUIREMENTS
FDA 483 – E. Main St. Little Falls, Dated 12/1/04 **6 Observations** **16 Examples Cited**	- Changes made to records without approval (2) examples	-25% of the manufacturing equipment not qualified (6) examples	-Lack of Cleaning Validation (2) examples -Production documentation is not controlled to prevent unauthorized changes (3) examples	-Unsecure computer records (3) examples	
1. FDA 483 – E. Main St. Little Falls – Dated 2/8/06 P-79 **7 Observations**	- Inadequate investigation of complaints – three (3 examples - Inadequate Complaint Procedure		-Control procedures are not established to validate the performance of manufacturing processes – two (2) examples		- Adverse drug experience (ADE) information has not been reported to the FDA - Adverse drug experiences not investigated - Adverse drug experience information not reviewed - Some ADEs were not reported to the FDA - Procedures not established for post marketing ADEs
2. FDA 483 – E. Main St. Little Falls – Dated 8/10/2006 Exhibit 8 **15 Observations**	QA failed to prevent the release of lots that had significant nonconformances, including: - Incomplete lab data - Batch that failed to meet specification - Batch record deviations - Manufacturing deviations QA filed to detect significant discrepancies in Quality reports and records, five (5) examples include: - Stability testing	-Examples of inadequate equipment preventive maintenance program	-Inadequate validation of the cleaning procedures for manufacturing equipment -Inadequate inprocess testing for four (4) examples -Deviations from production and process control procedures not justified for three (3) examples -Master product and control records are incomplete -Equipment qualification issues -Rejected in-process are not	-Seven (7) different product Quality Testing records were incomplete – Examples: -Changes entered into lab notebooks after it was approved -Original out of specification results for three (3) different products were not recorded -Lab computer system was not validated -Stability Testing Protocol not followed	

EVENT & LOCATION	QUALITY SYSTEM	FACILITIES & EQUIPMENT - SYSTEM	PRODUCTION SYSTEM	LABORATORY & CONTROL SYSTEM	REGULATORY REQUIREMENTS
	- Process Validation - Batch record Batch failures not investigated - Stability testing - Lab testing - Active ingredient uniformity of tablets		identified and controlled properly -Inadequate storage practices for chemical raw materials -Chemical raw material handling procedure not followed		
3. Warning Letter – E. Main St. – Little Falls – Dated 8/15/2006 P-229	FDA stated that Actavis: -"Several of the observed deficiencies were long-standing, and there is no indication of how or why the lack of compliance was not identified by your firm" -"why it was allowed to continue for such an extended period of item" -"Does your firm have any insight into this situation"? -Prior response to the FDA does not include details that were discussed during the inspection." -Prior response does not identify the cause of the observed deficiencies with regard to postmarking reporting requirements				
4. FDA 483 – Taft Road – October 2006 **3 Observations**				-Deviations not justified -Test Methods not properly validated -Suitability verification not conducted	
5. Mylan Audit Dated 12/04/06 M-24	-Shortage of qualified personnel	-Dated equipment -Warehouse leaking water -Ventilation system smelled of mildew		-Quality Control Lab congested	
6. Revised Warning Letter – E. Main St. Little Falls - Dated 2/1/2007 P-25	-Summarized the prior observations and emphasized the seriousness of the noncompliant observations -Actavis Corrective Action and is in disagreement: o FDA stated "In fact, we do not agree with assertions in your August 29 and 30, 2006 letter that certain of the observations listed on the FDA 483 are not accurate" o "..we are concerned about the quality of the of drug products that have been released from your facility under the serious lack of cGMP controls found during the inspection." o "Your response provides no assurance that the records and conditions of manufacture and testing of each such lot of drug products released and marketed by our firm will be evaluated to assure that the released drug products have their appropriate, identity, strength, quality, and purity."				
7. FDA 483 – E. Main St. Little Falls – Dated 9/28/2007 P-50			-Approved production and process procedures not followed	-Stability Testing Protocol not followed	-FDA required – Field Alert Report not submitted on time

EVENT & LOCATION	QUALITY SYSTEM	FACILITIES & EQUIPMENT - SYSTEM	PRODUCTION SYSTEM	LABORATORY & CONTROL SYSTEM	REGULATORY REQUIREMENTS
8. **FDA 483 – Riverview Drive – Dated 5/20/2008 P-26** **11 Observations** **95 Page Establishment Inspection Report**	-Procedures not followed -Responsibilities not followed -Released products not meeting specifications -Four (4) examples of not investigation products out of specification results -Four (4) examples of inadequate investigation into unexplained discrepancies			-Eleven (11) examples where products did not meet specifications throughout the products' labeled shelf life -Five (5) examples of lab controls do not include scientifically sound test procedures	
9. Actavis 5/20/2008 Memo to Senior Management – Summarizing the FDA Inspection	FDA Inspector stated "One person was signing of in multiple location and the batch (this occurred on the Digitek double tablet Investigation – The FDA Inspector considered it a very important Observation – additional review of this Investigation may have stopped the release of the batch FDA inspector stated that "from a Quality Systems standpoint, there was a Total Failure". Issues and needs (from FDA inspector): - Do not fix broken systems – get new systems - (Need) Improved infrastructure - Personnel - (Need) Philosophical Change - Investigations on the (past) 483 still not complete - Health hazards on recalls are delinquent - "Get very nervous when you tell us that you are releasing product using		FDA inspector stated that: -"premature to be releasing product" -"concerned about product still on the market that was made in Little Falls using similar systems that had failed" -"concern about the 48 products with no impurity profile"	-	

EVENT & LOCATION	QUALITY SYSTEM	FACILITIES & EQUIPMENT - SYSTEM	PRODUCTION SYSTEM	LABORATORY & CONTROL SYSTEM	REGULATORY REQUIREMENTS
	current Quality Systems -				
10. Consent Decree for Permanent Injunction Exhibit 214	-Inspected the firms facilities in Totowa, Little Falls and Taft Rd a total of eight (8) times. The FDA stated: -"drugs are adulterated" -"Interstate commerce drugs that are misbranded" -Introduce or deliver "new drugs that are neither approved" per regulations -"FDA's five inspections of Actavis Totowa's facilities over the last three years have revealed numerous and recurring violations of the current cGMP requirements for drugs"				